

A NEW SYNTHESIS OF α -IODO CARBOXYLIC ACID USING IODINE-COPPER SALT

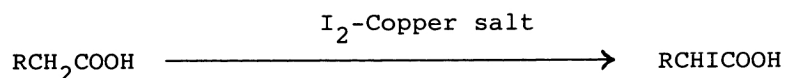
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Direct α -iodination of some carboxylic acids, namely, acetic acid, propionic acid, butyric acid, and valeric acid, using iodine-copper salt, gave the corresponding α -iodo carboxylic acid in high yield. This new synthetic method afforded several advantage over classical α -iodo carboxylic acid procedures.

Much work has been reported on the bromination¹⁾ and chlorination²⁾ of aliphatic acids. However, α -iodo acid is usually prepared by halogen interchange of a bromo compound with sodium iodide.³⁾ Recently, Harpp *et al.*⁴⁾ reported that the reaction of acyl halide with iodine gave the α -iodoacyl halide; and Rathke and Lindert⁵⁾ described a convenient method for the preparation of α -iodo ester using lithium ester enolate and iodine. However, no direct iodination of any carboxylic acid under acidic conditions has been reported in the literature up to the present time.

We have been investigating a novel iodination using iodine-copper(II) acetate; and as a first step in this research project, we reported earlier the α -iodination of ketones;⁶⁾ the regioselective iodination of estradiol, estriol, and estrone;⁷⁾ and iodination of electrone-rich aromatic compounds.⁸⁾ In the work described in these reports, we demonstrated that iodine-copper(II) acetate in acetic acid is a useful reagent for the syntheses of some iodo compounds. In the present paper, we would like to report that the α -iodination of carboxylic acid with some copper salts gave α -iodo carboxylic acid in good yield.



The reaction of acetic acid with iodine and copper(II) acetate under refluxing for 40 h gave iodoacetic acid; mp 82-84 °C (80%). In the case of propionic acid (for 50 h), 2-iodopropionic acid (70%) was also obtained. Since these reactions required a long time under refluxing conditions, we investigated the effects of some copper(I) and copper(II) salts.

A typical procedure is as follows. A mixture of acetic acid (1) (0.437 mol), iodine (14.1 mmol), and copper(II) acetate (14.1 mmol) was stirred in a nitrogen atmosphere under refluxing for 40 h. The precipitated copper(I) iodide was removed by filtration, and the unreacted acetic acid by reduced distillation. Crystallization of the residue from hexane gave iodoacetic acid (5) as plates (2.090 g), mp 82-84 °C.^{9a)} These results are summarized in Table 1 for the iodination of 1.

The observed reactivity order for these various copper(I) and copper(II) salts

[CuCl > CuOAc > CuCl₂·2H₂O > Cu(OAc)₂·H₂O] indicates that these compounds play an important role in the iodination of acetic acid.

Table 1. Effect of copper(I) and copper(II) salt on the iodination of acetic acid.

Copper salt (mol equiv.)	Time/h at reflux	Yield of iodoacetic acid/% ^{a)}
Cu(OAc) ₂ ·H ₂ O (1.0)	40	80
CuCl ₂ ·2H ₂ O (1.0)	13	72
CuCl (1.0)	5	68
CuOAc (1.0)	6	65
CuCl (0.5)-CuCl ₂ ·2H ₂ O (0.5)	6	95

a) Isolated yield based on iodine used.

The reactions of propionic acid (2), butyric acid (3), and valeric acid (4) with iodine-copper(I) chloride-copper(II) chloride at 120 °C yielded the corresponding α-iodo carboxylic acid in good yields. These results are summarized in Table 2.

Table 2. Efficient α-iodination of carboxylic acid using iodine (1.351 mmol)-copper(I) chloride (0.5 mol equiv.)-copper(II) chloride (0.5 mol equiv.) at 120 °C.

Materials	Time/h	Products	Isolated yield/% ^{a)}	Mp or bp/°C	Lit. mp or bp/°C
CH ₃ CH ₂ COOH (<u>2</u>)	6.0	CH ₃ CHICOOH (<u>6</u>)	90	43-44	43-44 ^{9b)}
CH ₃ CH ₂ CH ₂ COOH (<u>3</u>)	6.5	CH ₃ CH ₂ CHICOOH (<u>7</u>)	85	39-40	39-39.5 ^{9c)}
CH ₃ CH ₂ CH ₂ CH ₂ COOH (<u>4</u>)	7.0	CH ₃ CH ₂ CH ₂ CHICOOH (<u>8</u>)	85	109/7mmHg	109/7mmHg ¹⁰⁾

a) Isolated yield based on iodine used.

This is the first time that direct α-iodination of carboxylic acid has been successfully accomplished. It is particularly noteworthy that this reaction affords a new synthetic method for α-iodo carboxylic acid, more convenient than the method used heretofore.

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- 10) NMR (CCl₄): δ 1.00 ppm (t, 3H), δ 4.31 ppm (t, 1H), and δ 11.70 ppm (s, 1H). Found: *m/e* 227.9629. Calcd for C₅H₉O₂I: M, 227.9648.

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